

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

**Nityr nitisonone 2 mg
Nityr nitisonone 5 mg
Nityr nitisonone 10 mg**

Tablets

Composition:

Active ingredient:

Each tablet of Nityr 2 mg contains nitisonone 2 mg

Each tablet of Nityr 5 mg contains nitisonone 5 mg

Each tablet of Nityr 10 mg contains nitisonone 10 mg

For a list of inactive and allergenic ingredients in the preparation, see section 6 "Further Information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for the treatment of your ailment. Do not pass it on to others. It may harm them even if it seems to you that their ailment is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Nityr tablets is given to treat a hereditary disease called tyrosinemia type 1. In this disease, your body is unable to completely break down the amino acid tyrosine (amino acids are building blocks that build the proteins in our body), resulting in the body accumulating a substance that is harmful to it. Nityr tablets prevent the breakdown of the amino acid tyrosine in the first place, and as a result, the harmful substance does not accumulate in your body.

Because tyrosine remains in the body, a special dietary regimen based on foods with low amounts of tyrosine and phenylalanine should be maintained during treatment with Nityr tablets.

Therapeutic group: treatment of essential metabolic system defects.

2. BEFORE USING THE MEDICINE:

Do not use the preparation if:

- You are sensitive (allergic) to the active ingredient nitisonone or to any of the other ingredients contained in the medicine (please see section 6 "Further Information").
- You are breastfeeding.

Special warnings regarding use of the medicine

Before and during treatment with Nityr tablets, tell the doctor:

- If redness or any other sign occurs in the eyes, refer to the doctor immediately for an eye examination. Eye problems may indicate inadequate dietary control.

Tests and follow-up:

Before starting treatment and when using the medicine, an eye examination should be performed by an ophthalmologist. During the treatment period, you will be referred for blood tests to check if the treatment is effective and to make sure that there are no side effects that cause blood system disorders. Liver tests should be performed periodically, as tyrosinemia type 1 affects the liver.

You should go for a follow-up appointment with your doctor every six months. If side effects occur, shorter intervals between appointments are recommended.

Drug interactions

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell your doctor or pharmacist.

Nityr tablets may interfere with the effect of other medicines, such as:

- Epilepsy medications, such as phenytoin
- Blood anticoagulants, such as coumadin/warfarin

Use of the medicine and food:

If you start treatment with Nityr tablets, while taking it with food, it is recommended that you continue to take Nityr tablets with food throughout the whole treatment.

Pregnancy, breastfeeding and fertility:

The safety of Nityr tablets has not been tested in pregnant and breastfeeding women. Inform the attending doctor if you are planning to become pregnant. If you are pregnant, inform the doctor immediately.

Do not use the medicine while breastfeeding.

Driving and using machines:

When using this medicine there may be a minor effect that can impair alertness and therefore, caution is required when driving a vehicle when operating dangerous machinery and during any activity, that requires alertness.

During treatment, an effect on vision may occur. If you experience this, avoid driving or operating dangerous machinery until your vision returns to normal.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain regarding the dosage and treatment regimen of the preparation.

Treatment with Nityr tablets should be started under the instruction and supervision of a doctor experienced in the treatment of patients with hereditary tyrosinemia type 1.

The usual dose is: 1 mg/kg body weight per day. The doctor will adjust the dose for you individually.

It is advisable to administer the dose once daily.

However, since the data regarding patients weighing less than 20 kg are limited, it is recommended to divide the dose into two daily administrations for these patients.

If you have swallowing problems, the tablet can be crushed and mixed with water or applesauce.

Can be kept for 24 hours at room temperature if prepared with water.

Protect from direct sunlight.

Can be kept for two hours at room temperature if prepared with applesauce.

Protect from direct sunlight.

There is no need to put the applesauce mixture in the refrigerator.

Oral syringe administration instructions.

The suspension can be prepared in a syringe only with 1-2 tablets. Use only room-temperature water.

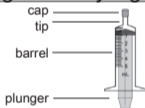
Use a 5 mL oral syringe with a cap to prepare one tablet.

Use only room-temperature water to prepare in a syringe.

Keep the suspension in the syringe at room temperature, out of direct sunlight, until use.

Discard the syringe after use.

Instructions for use using an oral syringe



Oral syringe

Preparing 1 tablet of Nityr with a 5 mL syringe

1. Remove the cap
2. Remove the plunger. Insert 1 Nityr tablet inside the syringe (Figure A)
3. Replace the plunger (Figure B)
4. Draw up 2.6 mL of room-temperature water into the syringe. There may be air in the syringe. Leave the air in the syringe (Figure C)
5. Place the cap on the tip of the syringe. Wait 60 minutes until dissolution (Figure D)
6. Turn the syringe up and down for at least 30 seconds (Figure E)
7. Make sure that the tablets have been broken into small pieces and the small pieces are evenly dispersed throughout the water to suspend (Figure F). Do not take the suspension if there are large pieces that are not evenly dispersed throughout the water. If there are large pieces, wait 10 minutes. Before giving the suspension, turn the syringe up and down to continue the process of dispersing the pieces in the suspension.
8. Remove the cap from the syringe (Figure G)
9. Insert the syringe into the mouth. If the patient is a child, insert the syringe into the inner cheek (Figure H)
10. Push down on the plunger until a small amount of air is left between the plunger and the tip of the syringe (Figure I). Do not release all of the air
11. Draw up an additional 2 mL of water into the syringe (Figure J)
12. Place the cap of the syringe. Shake the syringe for 10 seconds to disperse the remaining pieces throughout the water in the syringe (Figure K)
13. Remove the cap (Figure L)
14. Insert the syringe into the mouth. If the patient is a child, insert the syringe into the inner cheek (Figure M)
15. Push down on the plunger until the syringe is empty (Figure N). In case any pieces of the tablet are left, repeat steps 11-15

16. After use, rinse the syringe and dry it before using again.

Preparation of 2 Nityr tablets using an oral syringe

1. Remove the cap
2. Remove the plunger. Insert 2 Nityr tablets inside the syringe (Figure A)
3. Replace the plunger (Figure B)
4. Draw 5 mL of room-temperature water into the syringe. There may be air in the syringe. Leave the air in the syringe (Figure C)
5. Place the cap on the tip of the syringe. Wait 60 minutes until dissolution (Figure D)
6. Turn the syringe up and down for at least 30 seconds (Figure E)
7. Make sure that the tablets have been broken into small pieces and the small pieces are evenly dispersed throughout the water to suspend (Figure F). Do not take the suspension if there are large pieces that are not evenly dispersed throughout the water. If there are large pieces, wait 10 minutes. Before giving the suspension, turn the syringe up and down for 30 seconds to continue the process of dispersing the pieces in the suspension.
8. Remove the cap from the syringe (Figure G)
9. Insert the syringe into the mouth. If the patient is a child, insert the syringe into the inner cheek (Figure H)
10. Push down on the plunger until a small amount of air is left between the plunger and the tip of the syringe (Figure I). Do not release all of the air
11. Draw up an additional 2 mL of water into the syringe (Figure J)
12. Place the cap of the syringe. Shake the syringe for 10 seconds to disperse the remaining pieces throughout the water in the syringe (Figure K)
13. Remove the cap (Figure L)
14. Insert the syringe into the mouth. If the patient is a child, insert the syringe into the inner cheek (Figure M)
15. Push down on the plunger until the syringe is empty (Figure N). In case any pieces of the tablet are left, repeat steps 11-15

16. After use, rinse the syringe and dry it before using again.

Preparation of more than 2 tablets with an oral syringe

If you need to take more than 2 tablets, follow the instructions for preparation and administration of one tablet and the instructions for preparation and administration of 2 tablets. Do not add more than 2 tablets to a syringe.

Preparation and administration of Nityr tablets with applesauce

Crush only one tablet at a time

1. Put about one teaspoon of applesauce in a container.
2. Place a Nityr tablet onto a metal teaspoon.
3. Put a second teaspoon on it and crush the tablet.
4. Put the powder that has formed in the container with the applesauce.
5. If more than one tablet is needed, repeat steps 2-3 and put the powder in the container with the applesauce.
6. Mix the applesauce and the powder well.
7. Using a teaspoon, swallow the mixture.
8. Put another teaspoon of applesauce into the container and mix with the leftover powder. Repeat this step until no mixture is left in the container.
9. Transfer the mixture to a teaspoon and swallow the rest of the mixture.

Do not exceed the recommended dose

If you accidentally took a higher dosage, or if a child has accidentally swallowed the medicine, immediately refer to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take the medicine at the required time, do not take a double dose, take a dose at the regular time and consult the doctor.

Adhere to the treatment regimen as recommended by the doctor.

Do not stop taking the medicine or change the dosage without consulting your doctor, even if you think the medicine is not working properly.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS:

As with any medicine, use of Nityr tablets may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

If you notice any eye-related side effects, talk to your doctor immediately about the need for an eye exam. Treatment with nitisonone causes high levels of tyrosine in the blood that can cause eye-related symptoms. These effects are caused as a result of higher tyrosine levels.

Common side effects – effects that occur in 1-10 users in 100:

- Inflammation in the eye (conjunctivitis)
- Opacity and inflammation in the cornea (keratitis)
- Sensitivity to light (photophobia) and eye pain

Uncommon side effects – effects that occur in 1-10 users in 1000:

- Inflammation of the eyelid (blepharitis)

Additional side effects:

Common side effects – effects that occur in 1-10 users in 100:

- Reduced level of platelets (thrombocytopenia) and white blood cells (leukopenia), shortage of certain white blood cells (granulocytopenia).

Uncommon side effects – effects that occur in 1-10 users in 1000:

- Increased number of white blood cells (leucocytosis).
- Itching (pruritus), skin inflammations accompanied by skin peeling (exfoliative dermatitis) and rash.

If a side effect occurs, if one of the side effects worsens, or if you are suffering from a side effect not mentioned in the leaflet, consult with the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:

<https://sideeffects.health.gov.il>

5. HOW SHOULD THE MEDICINE BE STORED?

• Avoid poisoning! This medicine, and any other medicine, must be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.

• Do not use the medicine after the expiry date (exp. date) that appears on the external package. The expiry date refers to the last day of that month.

• Do not discard of medicines via wastewater or household waste. Ask the pharmacist how to discard of medicines you no longer use. These measures will help protect the environment.

Storage conditions

- Do not store above 25°C.
- May be used for up to two months after first opening.

6. FURTHER INFORMATION:

• In addition to the active ingredient nitisonone, the medicine also contains:

Lactose monohydrate, Glycerol Dibehenate

• What the medicine looks like and the contents of the package:

Off-white, flat, round tablets marked with the letter "L" on one side and the other side marked with the medicine dosage: 2 mg or 5 mg or 10 mg.

• Nityr tablets is marketed in packages of 60 tablets in plastic bottles with a child-resistant cap.

• **Registration holder and address:** Truemed Ltd., 10 Beni Gaon St., Poleg Industrial Park, P.O. Box 8105., South Netanya, Israel.

• **Name of manufacturer and address:** Cycle Pharmaceuticals Ltd., Cambridge, United Kingdom.

• Revised in January 2021 according to MOH guidelines.

• Registration number of the medicine in the National Drug Registry of the Ministry of Health: 165-37-35679, 165-38-35680, 164-95-35681